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PRINCIPAL INVESTIGATOR: Henry S. Sacks, M.D., Ph.D.

CONTRACTING ORGANIZATION: Mount Sinai School of Medicine  
New York, New York 10029

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## INTRODUCTION

The benefits and risks of hormone replacement therapy (HRT) for post-menopausal women have been studied extensively, and yet for most women the choice remains one of uncertainty. HRT is widely believed to decrease the future risk of coronary heart disease, osteoporosis, and stroke, but also it is widely believed to increase the future risk of breast and endometrial cancer. The addition of progestin to estrogen is believed to eliminate the increased risk of endometrial cancer, but may also lessen the preventive effect on coronary heart disease risk. HRT is also known to affect serum lipoproteins, sexual function, and urinary function, and it can cause endometrial hyperplasia and other adverse effects, and may require invasive monitoring procedures. Although the American College of Physicians and others have studied HRT and provide guidelines for women with a variety of risk factors, none of the recommendations apply to women with a history of breast cancer. In addition, the guidelines apply to population groups and not to individuals. Any individual may value a health state, an intervention, or the future risk of an illness differently than do others. Personal decisions regarding preventive medicine therefore should reflect these valuations.

It is widely believed that HRT is contraindicated in postmenopausal women who have had breast cancer. However, HRT has not been adequately studied among breast cancer survivors. The detection of early breast cancer has increased dramatically during the last decade accompanied with a rise in five year survival of treated patients, so there are many women who need guidance. There are approximately 182,000 new cases of breast cancer in women in the U.S. per year. Since the majority of these women will have localized disease can expect to survive 20 years or more, they will face risks of vascular and bone disease similar to those without a history of breast cancer. The induction of premature menopause with adjuvant chemotherapy increases the risk of coronary artery disease and osteoporosis among these women. The prohibition of HRT may diminish overall survival and quality of life among breast cancer survivors despite higher risk of endometrial and breast carcinoma with this intervention

Until the results of clinical trials of HRT in breast cancer survivors are available, which will take many years, it will remain uncertain as to whether this population of women should be given HRT. While we await such results, we are developing a decision analysis method utilizing a mathematical model to provide guidance for women with breast cancer as to whether they should take HRT.

## **BODY**

The goals of this project are to develop a computerized decision analysis model concerning the risks and benefits of hormone replacement therapy for breast cancer survivors.

During the first year, we updated our literature search and review and found numerous studies relevant to our question. We developed a pilot instrument to measure patient preferences, but found that this did not provide useful information. We have begun construction of two alternative decision analysis models. During the next year we plan to continue development of the model. Because of the complexities of developing valid instruments for measuring patient preferences (utilities), we have rearranged our budget to permit us to obtain the consultative services of Dr. Albert Wu of John Hopkins University, an authority on measurement of quality of life.

### **Results to date:**

As of October 29, after 6 weeks of recruitment at the Johns Hopkins site we have the following:

Total calls attempted: 122

# Unreachable	37	(Most not at home when called)
# No's	46	(Most not interested or won't have time)
# Ineligible	11	(Mostly not peri-post menopausal)
# Yes's	40	
# Interviews	28	(The rest did not show, or were ineligible)

21 interviews have been in the General Internal Medicine Clinic, and 7 in the Breast Cancer Clinic. For now we will continue recruiting as we have been, but are considering ways to increase recruitment in the breast center. For instance, we are thinking about loosening the eligibility criteria to include women up to 5 years after their last treatment for breast cancer (instead of the current 3 years).

## **CONCLUSIONS**

At this early stage in the project, we have not reached any conclusions.

## **REFERENCES**

1. American Cancer Society . Cancer Facts and Figures 1995; 1-29.
2. Weinstein MC, Fineberg HV. Clinical Decision Analysis. Philadelphia,PA: W.B. Saunders Co., 1980:1-351.
3. Gorsky RD, Koplan JP, Peterson HB, Thacker SB. Relative risks and benefits of long-term estrogen replacement therapy: a decision analysis. *Obstet Gynecol* 1994; 83:161-166.
4. Isaacs CJ, Swain SM. Hormone replacement therapy in women with a history of breast carcinoma. *Hematol Oncol Clin North Am* 1994; 8:179-195.
5. Hunt K, Vessey M, McPherson K. Mortality in a cohort of long-term users of hormone replacement therapy: an updated analysis. *Br J Obstet Gynaecol* 1990; 97:1080-1086.
6. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, Hennekens C, Rosner B, Speizer FE. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995; 332:1589-1593.
7. Gerhardsson de Verdier M, London S. Reproductive factors, exogenous female hormones, and colorectal cancer by subsite. *Cancer Causes Control* 1992; 3:355-360.
8. Furner SE, Davis FG, Nelson RL, Haenszel W. A case-control study of large bowel cancer and hormone exposure in women. *Cancer Res* 1989; 49:4936-4940.
9. Jacobs EJ, White E, Weiss NS. Exogenous hormones, reproductive history, and colon cancer (Seattle, Washington, USA). *Cancer Causes Control* 1994; 5:359-366.
10. Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR, Gapstur SM, Folsom AR. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control* 1994; 5:38-52.
11. Davis FG, Furner SE, Persky V, Koch M. The influence of parity and exogenous female hormones on the risk of colorectal cancer. *Int J Cancer* 1989; 43:587-590.
12. Peters RK, Pike MC, Chang WW, Mack TM. Reproductive factors and colon cancers. *Br J Cancer* 1990; 61:741-748.
13. Birge SJ. Is there a role for estrogen replacement therapy in the prevention and treatment of dementia? *J Am Geriatr Soc* 1996; 44:865-870.
14. Kuller LH. Hormone replacement therapy and its potential relationship to dementia. *J Am*

Geriatr Soc 1996; 44:878-880.

15. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banerjee S, Koenig KL, Shore RE, Strax P, Pasternack BS. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. *J Natl Cancer Inst* 1995; 87:190-197.
16. Cobleigh MA, Berris RF, Bush T, Davidson NE, Robert NJ, Sparano JA, Tormey DC, Wood WC, Breast Cancer Committees of the Eastern Cooperative Oncology Group . Estrogen replacement therapy in breast cancer survivors. A time for change. *JAMA* 1994; 272:540-545.
17. DiSaia PJ. Hormone-replacement therapy in patients with breast cancer. A reappraisal. *Cancer* 1993; 71:1490-1500.
18. Stoll BA. Hormone replacement therapy in women treated for breast cancer. *Eur J Cancer Clin Oncol* 1989; 25:1909-1913.
19. Baum M. Hormone replacement therapy and breast cancer. *Lancet* 1994; 343:53.
20. Consensus conference: Osteoporosis. *JAMA* 1984; 252:799-802.
21. Crilly RG, Horsman A, Marshall DH, Nordin BE. Post-menopausal and corticosteroid-induced osteoporosis. In: Lauritzen C, Van Keep PA, eds. *Frontiers in hormone research: Estrogen therapy, the benefits and risks*. 5th ed. Basel: Front.Horm.Res., 1978:53-70.
22. Gallagher JC, Melton LJ, Riggs BL, Bergstrath E. Epidemiology of fractures of the proximal femur in Rochester, Minnesota. *Clin Orthop* 1980; 163-171.
23. Vassilopoulou-Sellin R. Estrogen replacement therapy in women at increased risk for breast cancer. *Breast Cancer Res Treat* 1993; 28:167-177.
24. Iskrant AP. The etiology of fractured hips in females. *Am J Public Health* 1968; 58:485-490.
25. Bollet AJ, Engh G, Parson W. Epidemiology of osteoporosis. *Arch Intern Med* 1965; 116:191-194.
26. Gyepes M, Mellias HZ, Katz I. The low incidence of fracture of the hip in the negro. *JAMA* 1962; 181:1073-1074.
27. Solomon L. Osteoporosis and fracture of the femoral neck in the South African Bantu. *J Bone Joint Surg* 1968; 50(B):2-5.
28. Solomon L. Bone density in ageing Caucasian and African populations. *Lancet* 1979; 2:1326-1330.



29. Farmer ME, White LR, Brody JA, Bailey KR. Race and sex differences in hip fracture incidence. *Am J Public Health* 1984; 74:1374-1380.
30. Marchant DJ. Estrogen-replacement therapy after breast cancer. Risks versus benefits. *Cancer* 1993; 71:2169-2176.
31. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991; 20:47-63.
32. The Writing Group for the PEPI Trial . Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995; 273:199-208.
33. Weinstein MC. Estrogen use in postmenopausal women--costs, risks, and benefits. *N Engl J Med* 1980; 303:308-316.
34. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, Ernster VL, Cummings SR. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992; 117:1016-1037.
35. Eden JA. Oestrogen and the breast. 2. The management of the menopausal woman with breast cancer. *Med J Aust* 1992; 157:247-250.
36. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med* 1991; 151:75-78.
37. Criqui MH, Suarez L, Barrett-Connor E, McPhillips J, Wingard DL, Garland C. Postmenopausal estrogen use and mortality. Results from a prospective study in a defined, homogeneous community. *Am J Epidemiol* 1988; 128:606-614.
38. Bergkvist L, Adami HO, Persson I, Bergstrom R, Krusemo UB. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progestogen replacement therapy. *Am J Epidemiol* 1989; 130:221-228.
39. Gambrell RD, Jr.. Proposal to decrease the risk and improve the prognosis of breast cancer. *Am J Obstet Gynecol* 1984; 150:119-132.
40. Wile AG, Opfell RW, Margileth DA. Hormone replacement therapy in previously treated breast cancer patients. *Am J Surg* 1993; 165:372-375.
41. Theriault RL, Sellin RV. A clinical dilemma: estrogen replacement therapy in postmenopausal women with a background of primary breast cancer. *Ann Oncol* 1991; 2:709-717.

42. Davidson JA. The need for a randomised trial of hormone replacement therapy in women with breast cancer. *Med J Aust* 1992; 157:429.
43. Lau J, Pauker SG. Extended techniques in decision analysis. *Proceedings of the symposium for computer applications* 1985; Ninth annual edition:193-197.
44. Lau J, Kassirer JP, Pauker SG. Decision Maker 3.0. Improved decision analysis by personal computer. *Med Decis Making* 1983; 3:39-43.
45. Kassirer JP, Moskowitz AJ, Lau J, Pauker SG. Decision analysis: a progress report. *Ann Intern Med* 1987; 106:275-291.
46. Sacks HS, Rose DN, Chalmers TC. Should the risk of acquired immunodeficiency syndrome deter hepatitis B vaccination? A decision analysis. *JAMA* 1984; 252:3375-3377.
47. Sacks HS, Rose DN. Zidovudine prophylaxis for persons with accidental percutaneous blood exposure: A decision analysis. *J Gen Intern Med* 1990; 5:132-137.
48. Wiesel J, Rose DN, Silver AL, Sacks HS, Bernstein RH. Lumbar puncture in asymptomatic late syphilis. An analysis of the benefits and risks. *Arch Intern Med* 1985; 145:465-468.
49. Felman YM. Lumbar puncture in asymptomatic neurosyphilis. (Editorial). *Arch Intern Med* 1985; 145:422-423.
50. Comstock GW. Prevention of tuberculosis among tuberculin reactors: maximizing benefits, minimizing risks [editorial]. *JAMA* 1986; 256:2729-2730.
51. Rose DN, Schechter CB, Sacks HS. Influenza and pneumococcal vaccination of HIV-infected patients: a policy analysis. *Am J Med* 1993; 94:160-168.
52. Singh P, Rose DN, Sacks HS. Rifabutin prophylaxis for prevention of mycobacterium avium infection. Decision analysis and cost-effectiveness analysis. Presented at the 2nd International Conference on Human Retroviruses and Related infections (Washington D C ) 1995; (abstract)
53. Insua JT, Sacks HS, Lau TS, Reitman D, Pagano D, Chalmers TC. Drug treatment of hypertension in the elderly. A meta-analysis and qualitative review. *Ann Intern Med* 1994; 121:355-362.
54. Gross P, Hermogenes A, Sacks HS, Lau J, Levandowski RA. The protective efficacy of influenza vaccine in the elderly. A meta-analysis. *Ann Intern Med* 1995; 123:518-527.
55. Cowen ME, Chartrand M, Weitzel WF. A Markov model of the natural history of prostate cancer. *J Clin Epidemiol* 1994; 47:3-21.

56. Fleming C, Wasson JH, Albertsen PC, Barry MJ, Wennberg JE. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. Prostate Patient Outcomes Research Team [see comments]. JAMA 1993; 269:2650-2658.
57. Dickersin K, Hewitt P, Mutch L, Chalmers I, Chalmers TC. Perusing the literature: comparison of MEDLINE searching with a perinatal trials database. Controlled Clin Trials 1985; 6:306-317.
58. Stiggelbout AM, De Haes JCJM, Kiebert GM, Kievit J, Leer JH. Tradeoffs between quality and quantity of life. Med Decis Making 1996; 16:184-192.
59. Levine MN, Gafni A, Markham B, MacFarlane D. A bedside decision instrument to elicit a patient's preference concerning adjuvant chemotherapy for breast cancer. Ann Intern Med 1992; 117:53-58.